Docket No.: 381092000720
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:
Terry P. SNUTCH et al.

Application No.: 09/346,794 | Confirmation No.: 2888

Filed: July 2, 1999 | Art Unit: 1646

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS | Examiner: Nirmal Singh Basi

REPLY BRIEF UNDER 37 C.F.R. § 41.41

MS Appeal Brief – Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Brief is in Reply to the Examiner's Answer mailed 29 November 2005, setting a deadline for this Reply Brief of 29 January 2006. As 29 January 2006 fell on a Sunday, this correspondence is timely filed.

Appellants have submitted an amendment to cancel claims 25-27 and 34 to simplify argument. Appellants believe this amendment will be entered as a matter of right as set forth in 37 C.F.R. § 41.33(b)(1). A copy of this amendment is enclosed as Exhibit 1.

The sole basis for rejection is an asserted lack of utility under 35 U.S.C. § 101.

The present claims, directed to a screening test for antagonists of the activity of a molecule known to mediate a specific disease meets the utility standard required by the statute.

The position taken by the Examiner appears to be that unless the screening test claimed has already resulted in identifying a compound that is shown to treat one of the conditions stated in the specification or known in the art, no sufficient utility is shown. "There is no disclosure of even a single agonist that stimulates channel activity or an antagonist that reduces channel activity." (Examiner's Answer page 3, third to last line). This is not relevant to the claims appealed, since the claims are not directed to a method of treating a condition mediated by T cell activity, but rather to a method to discover compounds that would be thus useful. The method of the invention is a research tool, not a method of treating diseases.

Research tools are acknowledged as patentable if their use is directed to discovery of the properties of other materials, not to discovery of their own properties. This was made clear most recently in the majority opinion in *In re Fisher*, 421 F3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The claims in that case were to express sequence tags (EST's) obtained from cDNA libraries of maize. The nature of the proteins encoded by the genes represented by the EST's was unknown, as was their function. The majority distinguished the utility of such compositions from research tools such as microscopes as follows:

> A microscope has the specific benefit of optically magnifying an object to immediately reveal its structure. One of the claimed EST's, by contrast, can only be used to detect the presence of genetic material having the same structure as the EST itself. It is unable to provide any information about the overall structure, let alone the function of the underlying gene. Accordingly, while a microscope can offer an immediate real-world benefit in a variety of applications, the same cannot be said for the claimed EST's.

(The dissent found that the EST's themselves had sufficient utility).

In accordance with the above-quoted statement from the majority opinion, the method of the invention does not simply result in a further definition or characterization of the T-type channel itself. Rather, the method assesses the characteristics of, for example, the members of combinatorial libraries of compounds or individual compounds unrelated to the T-type channel used in the method claimed. Like the microscope, it reveals something about something else, where what it reveals about the "something else" is itself useful.

This meets the standard of *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) where claims were drawn to a process to prepare a compound whose function was not known. Unlike the situation in *Brenner*, the function of the compounds identified by the method of the invention is known. The antagonist thus identified can be used to treat conditions specified in the application and attested to by declaratory evidence.

Appellants are aware of no jurisprudence which rejects as lacking sufficient utility claims to research methods that are designed to characterize the properties of useful materials. This is consistent with the Guidelines of the Patent Office itself as outlined in the Brief.

Appellants again emphasize that the claims in the present application are not directed to methods to treat the conditions set forth in the specification; they are directed to methods to identify compounds that are candidates for such treatment. Such identification methods are used every day in the pharmaceutical industry to provide small molecule drug candidates. Evidently, the industry finds these methods quite useful. There is no requirement in the statute that the method of the invention directly benefit patients; it must simply be useful in a real-world sense.

There Is No Question that SEQ ID NO: 23 Encodes a T-Type Calcium Ion Channel.

This point has already been made, but evidently ignored. Example 5 clearly shows that HEK cells transfected with, and expressing, the cDNA of SEQ ID NO: 23 show the activity of a T-type channel. There is no criticism that this experiment is somehow flawed. Rather, the documents cited by the Examiner putatively call into question the reliability of determining functionality based on homology. Because homology was not relied on, they are irrelevant. The functionality of SEQ ID NO: 23 as encoding a T-type channel has been directly demonstrated in a working example. The working example also describes methods for determining this functionality and it is noted that with respect to nucleotide sequences that hybridize under the specified conditions to SEQ ID NO: 23, these must also encode a protein functional as a T-type calcium ion channel, otherwise they are not in the claim. Verification that this is the case is readily performed as taught in Example 5 of the specification. Appellants fail to see how there can be any question that the claims are limited to the use of cells that actually express T-type calcium ion channels.

The Nexus Between Abnormally High T-type Channel Activity and Specified Disease Conditions is Established on the Record.

Appellants have submitted multiple documents to confirm this.

Exhibit A attached to the Appeal Brief filed on 13 September 2005, shows that as early as 1997, well before the application date herein, mibefradil, a calcium antagonist that blocks selectively the T-type calcium channel, was known to be effective in reducing blood pressure as demonstrated in the clinic. This article, alone, establishes that at least one of the conditions specified on page 9 of the specification, second full paragraph, is associated with T-type calcium ion channel mediation.

Exhibit B, a 1996 article, demonstrates that mibefradil was considered sufficiently promising to be tested in the clinic in patients with chronic congestive heart failure.

Exhibit C is a 1996 article that reports that intravenous mibefradil produced an overall favorable cardiovascular response in patients with varying degrees of left ventricular systolic dysfunction.

Exhibit D is a 1996 article describing experiments in dogs which show that mibefradil is a dilator of large and small coronary arteries.

Exhibit E is a 1996 article demonstrating that mibefradil prevents stroke in a rat model.

Exhibit F demonstrates that mibefradil prevents proliferation of smooth muscle cells in a rat model so as to prevent neointima formation after vascular injury.

Exhibit G is a 1996 article demonstrating that T-type calcium channels are abnormally expressed in diabetic mice, thus implying that antagonism would be helpful in treating diabetes.

Exhibit H is a 1996 article describing an *in vitro* experiment showing that another T-type channel-specific inhibitor, zonisamide, inhibits the spread of seizure activity.

The Examiner's Answer appears to ignore all this and relies on a review article by Ertel from which he selectively quotes. And the quotes do not seem particularly germane. The failure of certain calcium ion channel antagonists to be sufficiently specific to be T cell markers is really neither here nor there with regard to whether antagonists identified by the method of the invention would be specific. The variability of effects depending on concentration asserted to be associated with nifedipine seems equally irrelevant. Taken as a whole, the Ertel article appears to show that the association of T-type channels with particular conditions is fairly well established.

For example, page 41, column 1, states that

> Blocking these channels would be very advantageous in hypertensive therapy because of the resulting reduction in circulating catecholamines.
>
> Another system where a role for T-channels is fairly clear is in the generation of rhythmic activity in some neuronal structures; indeed, anticonvulsants are probably the most prolific therapeutic field for T-channel blockers. (Page 41, column 2.)
>
> The partial block (about 30-40%) of T-channels by antiepileptics or their partial inactivation by slight depolarization reduce bursting possibility do not affect the morphology of the bursts, notably the initial calcium dependent spike...partial block or inactivation does not prevent the absolute production of bursts although it reduces the bursts likelihood. (Page 41, column 2.)

As a report of a general discussion, one might expect that both these certainties and uncertainties of the nexus between T-type channels and specific conditions would be brought forward. This is not a perfect world, and there is no perfect pharmaceutical. If a "slam-dunk" relationship between a target and a disease condition were a prerequisite for a useful drug, there would be no useful drugs for any chronic conditions – the last useful pharmaceuticals would have been the antibiotics.

Appellants are certain the Board is aware that a nexus is required only between T-type channels and one of the conditions set forth in the specification or otherwise known in the art. *Raytheon Co. v. Roper Corp.*, 724 F2d 951, 220 USPQ 592 (Fed. Cir. 1983). If the Patent Office believes that other listed conditions in the specification are incredible or misleading, the Office is within its authority to require removal of references to these conditions. *In re Hozumi*, 226 USPQ 353 (Commissioner of Pat. and Trademarks 1985), but not to reject the claims on this basis.

The Examiner's Answer does not address the Declaration of Dr. Snutch, except to state that it is not persuasive. A review of this Declaration, however, both establishes Dr. Snutch's expertise in the field and verifies the association of T-type channels with specific conditions, including hypertension, neurological diseases and impaired fertility. This authority cannot just be dismissed. The Examiner appears to rely on acknowledged diversity in structure (slight) and distribution of the T-type channels. However, Dr. Snutch makes very clear that the claimed assay would be useful regardless of the location or exact structure of the T-type channel associated with the condition to be treated because the binding characteristics of the T-type channels, whatever their subtle differences, and wherever they may occur, are substantially identical.

The asserted teaching of Williams (1992) that various L-type channels control diverse functions such as neurotransmitter release, excitability and differentiation, does not appear germane to the present argument. It may be that T-type channels control diverse functions; what Dr. Snutch's Declaration says is that the method of the invention will identify antagonists with respect to all of these functions.

Finally, art blessed by the Patent Office itself establishes the nexus between T-type channels and various conditions. U.S. patent 6,358,706 ('706) has a filing date essentially contemporaneous with that of the present invention; U.S. 6,309,858 ('858) has a § 102(e) date almost a year earlier, and would be citable with respect to the present claims. Both of these documents disclose clearly that there is a nexus between T-type calcium channel activity and specified conditions. See, for example, column 6 of the '706 patent, lines 32-49. See, for example, column 2 of the '858 patent, lines 6-13.

Again, Appellants emphasize that they are not citing these patents as precedent requiring the grant of the present claims; they are citing these patents as literature providing evidence that the assertions of specific conditions with T-type activity as disclosed in the present application were well known in the art at the time the application was filed.

Summary and Conclusion

The present claims are directed to a method to identify antagonists of T-type calcium ion channel activity. The Examiner makes no assertion that the Appellants have not shown how to conduct the method; instead, the Examiner asserts that (1) the protein expressed by the specified nucleotide sequence may not be a T-type channel; (2) the specification does not name any compounds identified by the method or any compounds that are already known to antagonize T-type channels and (3) that inhibitors of T-type channels are not useful because the art does not recognize a nexus between T-type channel antagonism and the treatment of any condition.

As to the first contention, there is experimental evidence in the specification that SEQ ID NO: 23 does indeed encode a T-type channel; sequences that hybridize under the specified stringent conditions, in order to be included within the scope of the claims, must, by the explicit terms of the claim, function as T-type channels (which could be demonstrated in the same manner as was done for SEQ ID NO: 23 itself).

As to the second issue, it should be sufficient to point out that the claims are not directed to a method to use any compounds identified by the method of the invention; the claims are drawn to methods to identify compounds. This is not a University of Rochester (*University of Rochester v. G. D. Searle & Co.*, 358 F3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004) Cert. denied) problem. (Indeed, screening claims using Cox-2 were not invalidated by the *Rochester* Court.)

As to the third issue, Appellants have supplied a multiplicity of documents showing that the connection between T-type antagonism and specified conditions was well accepted in the art at the time of filing. Against this evidence, the Examiner has cited only a discussion at a 1997 meeting which, in fact, acknowledges certain of these connections. As to the asserted diversity of distribution of T-type channels, this was addressed by the Declaration of Dr. Snutch, an acknowledged expert in this field, who points out that this diversity is irrelevant to the validity of the assay, a point apparently not understood by the Examiner.

In view of the foregoing, Appellants respectfully request that the rejection of claims 28-31, 37 and 40 be reversed and these claims be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Dated: January 30, 2006

Respectfully submitted,

By S. Snutch Reg No. 39,183
for Kate H. Murashige
Registration No.: 29,959
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
(858) 720-5112

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	5

Application Number	09/346,794
Filing Date	July 2, 1999
First Named Inventor	Terry P. SNUTCH
Art Unit	1646
Examiner Name	Nirmal Singh Basi
Attorney Docket Number	381092000720

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply (Under 37 C.F.R. §§ 1.116 / 41.33 - 4 pages)
  - [x] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Return Receipt Postcard

Remarks

CUSTOMER NO.: 25225

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	MORRISON & FOERSTER LLP		
Signature	Michael G. Smith MICHAEL G. SMITH, Reg. No. 44,422		
Printed name	for Kate H. Murashige		
Date	January 26, 2006	Reg. No.	29,959

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: January 26, 2006 Signature: Judy Calem (Judy Calem)

sd-299264

Docket No.: 381092000720
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Terry P. SNUTCH et al.

Application No.: 09/346,794 | Confirmation No.: 2888

Filed: July 2, 1999 | Art Unit: 1646

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS | Examiner: Nirmal Singh Basi

AMENDMENT UNDER 37 C.F.R. §§ 1.116 / 41.33

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please cancel claims 25-27 and 34.

Claims directed to identifying agonists, specifically, of the T-type calcium channel, have been canceled as permitted by 37 C.F.R. § 41.33(b)(1) to simplify arguments on appeal. Applicants reserve the right to file a continuing application with regard to this subject matter.

CLAIM AMENDMENTS

1-27. (canceled)

28. (previously presented): A method to identify an antagonist of a T-type calcium channel which method comprises:

a) contacting a recombinant cell expressing the α_1 subunit of a heterologous T-type calcium channel with a known agonist of said T-type calcium channel;

b) contacting said cell with a compound to be tested; and

c) determining the ability of said compound to diminish the activation of said α_1 subunit by said agonist;

wherein said α_1 subunit is functional as a T-type calcium ion channel and is encoded by a nucleotide sequence which hybridizes under conditions of stringency corresponding to washing at 62° C in 0.2 x SSPE/0.1% SDS to a nucleic acid comprising SEQ ID NO: 23 and

wherein said activating comprises enhancing the flow of calcium ions into said cell in the presence as compared to the absence of said agonist;

whereby a compound which diminishes the activation of said α_1 subunit by said agonist is identified as an antagonist.

29. (previously presented): The method of claim 28 wherein said activation is measured by measuring the current through the calcium channel before and after said contacting of said cell with said compound.

30. (previously presented): The method of claim 28, wherein said cells contain a fluorescent dye sensitive to intracellular calcium concentration and said activation is determined by observing a change in the fluorescence of said dye when said contacting is performed.

31. (previously presented): A method to prescreen compounds as agonists or antagonists of T-type calcium ion channels by virtue of their ability to bind said T-type channels which method comprises:

a) contacting a recombinant cell expressing the α_1 subunit of a heterologous T-type calcium channel with a compound to be tested; and

b) determining the ability of said compound to bind to said cell expressing said α_1 subunit;

wherein said binding is determined by observing competitive binding with a known agonist or antagonist of said channel;

wherein said α_1 subunit is functional as a T-type calcium ion channel and is encoded by a nucleotide sequence which hybridizes under conditions of stringency corresponding to washing at 62°C in 0.2 x SSPE/0.1% SDS to a nucleic acid comprising SEQ ID NO: 23,

whereby a compound which is determined to bind said cell is identified as a compound which will behave as either an agonist or antagonist of a T-type calcium channel.

32-36. (canceled)

37. (previously presented): The method defined in claim 28 wherein the nucleic acid comprises SEQ ID NO: 23.

38-39. (canceled)

40. (previously presented): The method defined in claim 31 wherein the nucleic acid comprises SEQ ID NO: 23.

41-42. (canceled)

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Dated: January 26, 2006

Respectfully submitted,

Michael G Smith

By MICHAEL G SMITH, Reg. No. 44,422

FOR Kate H. Murashige
Registration No.: 29,959
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
(858) 720-5112